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Enolboration. 5. An Examination of the Effects of Amine, Solvent, and Other Reaction Parameters on the Stereoselective Enolboration of Ketones with Various Chx_2BX Reagents. An Optimized Procedure to Achieve the Stereoselective Synthesis of *E* Enol Borinates from Representative Ketones Using Chx_2BCl/Et_3N

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ABSTRACT

The effects of amine, solvent, concentration, temperature and other reaction parameters in controlling the enolate geometry have been systematically investigated in the present study. A ^{11}B NMR study of the interaction of representative tertiary amines of variable steric requirements with dicyclohexylchloroborane, Chx_2BCl, suggests that the smaller amines coordinate strongly with Chx_2BCl, while the more bulky amines do not. These amines have also been examined for the enolboration of diethyl ketone with Chx_2BCl, in order to understand the effect of the steric requirements of the amine on the enolate geometry. While the smaller amines favor formation of *E* enol borinate, the more hindered amines favor formation of the isomeric *Z* enol borinate. Triethylamine and *N,N*-diisopropylethylamine, the best amines selected in terms of yield and selectivity, have also been compared for the enolboration of two model ketones, diethyl ketone and propiophenone, using various Chx_2BX reagents (X = Cl, Br, I, OMs and OTf) to understand their effect with different ketones and reagents. Detailed studies for the enolboration of diethyl ketone with Chx_2BCl/Et_3N, with the hope of understanding the various effects on the enolate geometry and of improving the *E* enolate selectivity, suggest that formation of the *E* enolates are highly favored in non-polar solvents and in dilute medium, whereas the corresponding *Z* enolates are more favored in polar solvents and in relatively concentrated medium. The other reaction parameters, such as the enolization and the aldolization temperatures, and the order and the rate of addition of the various substrates, have essentially no influence on the stereochemistry. However, the aldolization at –78 °C for 2 h without allowing the reaction mixture to warm to room temperature improves the anti aldol selectivity. An understanding of these various effects in controlling the stereochemistry of the enolboration and the achievement of the selective synthesis of *E* enol borinates from representative ketones using Chx_2BCl/Et_3N under optimized reaction conditions are emphasized in this exploratory study.

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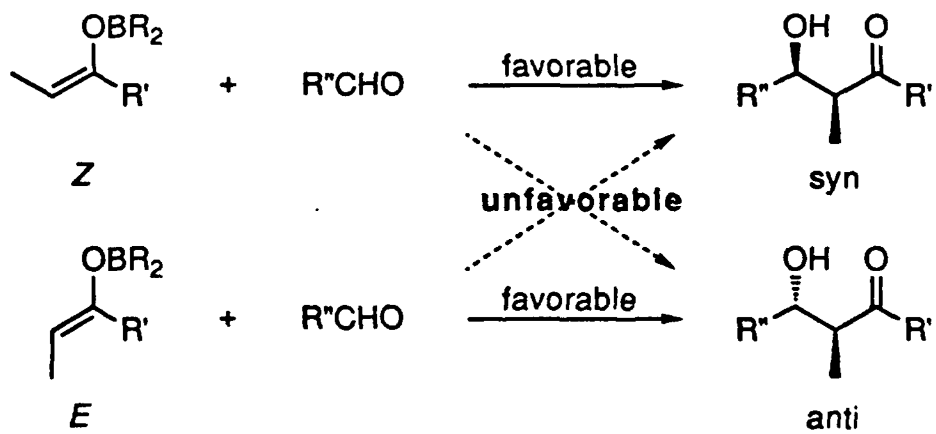
The effects of amine, solvent, concentration, temperature and other reaction parameters in controlling the enolate geometry have been systematically investigated in the present study. A ^{11}B NMR study of the interaction of representative tertiary amines of variable steric requirements with dicyclohexylchloroborane, Chx_2BCl, suggests that the smaller amines coordinate strongly with Chx_2BCl, while the more bulky amines do not. These amines have also been examined for the enolboration of diethyl ketone with Chx_2BCl, in order to understand the effect of the steric requirements of the amine on the enolate geometry. While the smaller amines favor formation of *E* enol borinate, the more hindered amines favor formation of the isomeric *Z* enol borinate. Triethylamine and *N,N*-diisopropylethylamine, the best amines selected in terms of yield and selectivity, have also been compared for the enolboration of two model ketones, diethyl ketone and propiophenone, using various Chx_2BX reagents (X = Cl, Br, I, OMs and OTf) to understand their effect with different ketones and reagents. Detailed studies for the enolboration of diethyl ketone with Chx_2BCl/Et_3N, with the hope of understanding the various effects on the enolate geometry and of improving the *E* enolate selectivity, suggest that

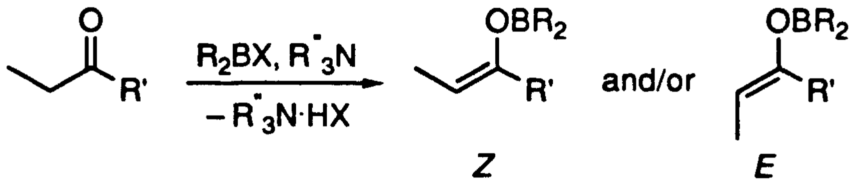
formation of the *E* enolates are highly favored in non-polar solvents and in dilute medium, whereas the corresponding *Z* enolates are more favored in polar solvents and in relatively concentrated medium. The other reaction parameters, such as the enolization and the aldolization temperatures, and the order and the rate of addition of the various substrates, have essentially no influence on the stereochemistry. However, the aldolization at –78 °C for 2 h without allowing the reaction mixture to warm to room temperature improves the anti aldol selectivity. An understanding of these various effects in controlling the stereochemistry of the enolboration and the achievement of the selective synthesis of *E* enol borinates from representative ketones using Chx_2BCl/Et_3N under optimized reaction conditions are emphasized in this exploratory study.

Stereoselective enol borinates are valuable intermediates in organic synthesis.[1] Their high reactivity and the stereoselectivity contribute greatly to the value of the aldol reaction.[2–7] It has been well documented that *Z* enol borinates give syn aldols and *E* enol borinates give anti aldols stereoselectively[3b] (Scheme I). It is, therefore, highly desirable to achieve the selective synthesis of either *Z* or *E* enol borinates.

Scheme I



Many methods have been developed for the generation of enol borinates.[8-10] One of the best, developed by Mukaiyama,[2] involves the reaction of ketones with R_2BX reagents containing a good leaving group (X = OTf) in the presence of a suitable tertiary amine, R''_3N (eq 1).



(1)

A current research project is directed toward examining the stereoselective generation of enol borinates in the hope of achieving an understanding of the factors influencing the enolate geometry. We have already established important influences of both the steric and electronic requirements of the alkyl and the leaving groups on boron on the enolate geometry.[7]

The steric requirements of the amine also influence the regioselectivity[2b] as well as the enolate stereochemistry.[3,5a] Smaller amines favor formation of kinetic enolates, while bulkier amines favor formation of thermodynamic enolates. Studies involving the use of Et_3N, a smaller amine, and *i*-Pr_2EtN, a bulkier amine, favoring the opposite enolate geometry, resulting in the stereoselective synthesis of either syn or anti aldols respectively, have also been reported for the aldolization of the enol borinates derived from oxazolidinone using *n*-Bu_2BOTf and aromatic aldehydes.[11] However, such a selectivity has been demonstrated only for this particular system.

The solvent polarity also plays a vital role in the reaction selectivity. In the case of enolboration, the effect of solvent has been studied using the widely employed R_2BOTf reagents.[3b] R_2BCl reagents, however, belong to a new class of organoboron reagents introduced recently to the field of enolboration favoring the stereoselective synthesis of *E* enol borinates.[5a] It has been demonstrated that the triflate and the chloride reagents behave differently, providing enol borinates with opposite enolate geometry. Therefore, it appeared highly desirable to do a systematic study of the effects of various factors, such as amine, solvent, concentration, temperature, and other reaction parameters, with this new class of organoboron chloride reagents.

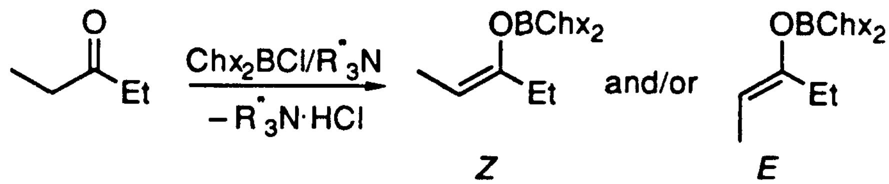
The selective generation of *E* enolates has long been a desired goal. Dicyclohexylchloroborane, Chx_2BCl, produces *E* enol borinates either exclusively or predominantly from various ketones.[6,7] This reagent has also been used by many workers to achieve the selective synthesis of anti aldols from representative α-chiral ethyl ketones and aldehydes via *E* enol borinates.[12,13] Ever since its original discovery, our study of Chx_2BCl/Et_3N has been directed toward achieving the synthesis of *E* enol borinates essentially exclusively from a variety of ketones. The present study, therefore, was designed to attain an understanding of the factors influencing the enolate geometry with the hope of achieving synthesis of *E* enol borinates from representative ketones using Chx_2BCl/Et_3N.

Results and Discussion

In the present study, a series of aliphatic tertiary amines of variable steric requirements, such as *N,N*-dimethylethylamine (Me_2EtN), *N,N*-diethylmethylamine (Et_2MeN), triethylamine (Et_3N), *N,N*-diethylisopropylamine (Et_2*i*-PrN), *N,N*-diisopropylethylamine (*i*-Pr_2EtN), and triisopropylamine (*i*-Pr_3N), were selected to achieve an understanding of the effect of the steric requirements of the amine on the enolate geometry in the enolboration of diethyl ketone with Chx_2BCl/R''_3N. A systematic ^{11}B NMR study was also carried out to understand the nature of the interaction of these amines with Chx_2BCl.

Et_3N and *i*-Pr_2EtN, the best amines selected in terms of yield and selectivity, were compared for the enolboration of two model ketones, diethyl ketone, an aliphatic ethyl ketone, and propiophenone, an aromatic ethyl ketone, using representative Chx_2BX reagents (X = Cl, Br, I, OMs and OTf) in order to understand the differences in the influence of the steric requirements of the amine with different ketones and reagents. Systematic studies have also been carried out to understand the effect of solvent, concentration, temperature, order and the rate of addition of substrates on the stereochemistry of the enolboration process with an aim to improve the selectivity for the synthesis of *E* enol borinates with Chx_2BCl/Et_3N. The new optimized procedure has also been employed for the enolboration of representative ketones to achieve the selective synthesis of *E* enol borinates.

Effect of Steric Requirements of Amine. It has been reported in the literature that the smaller amines, such as pyridine, DABCO, DBU and tetramethylguanidine, complex strongly with R_2BOTf reagents and, therefore, are totally ineffective for enolboration.[3] In the present study, a systematic ^{11}B NMR study on the interaction of representative tertiary amines of variable steric requirements with Chx_2BCl and also a detailed study on the effect of amine on the enolate geometry in the enolboration of diethyl ketone (eq 2) have been carried out. Both the ^{11}B NMR and the stereochemical results are summarized in Table I.



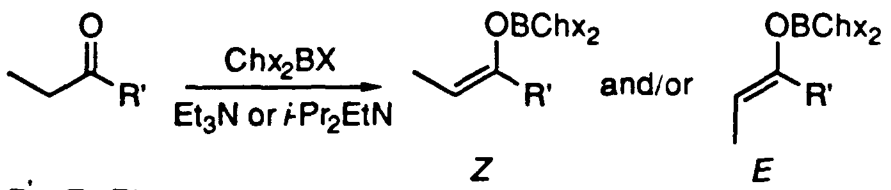
(2)

The ^{11}B NMR data in Table I clearly show that Me_2EtN, an amine with smaller steric requirements, coordinates strongly with Chx_2BCl at 0 °C, whereas the majority of the tertiary amines examined (higher homologues of Me_2EtN) do not coordinate at all. On the other hand, it has been reported based on a ^1H NMR study that even the highly hindered i-Pr_2EtN complexes with n-Bu_2BOTf completely at 25 °C within 30 min.[3] The poor Lewis acidity of Chx_2BCl, as compared to n-Bu_2BOTf, combined with the relatively greater steric requirements of the cyclohexyl groups, may contribute to the non-complexation of these amines. As the result, Chx_2BCl becomes a versatile reagent which can effect the enolization in the presence of a wide variety of tertiary amines of variable steric requirements. The yield of enol borinates can also be related to the steric requirements of the amine used for enolization. In the case of smaller amines, such as Me_2EtN, instead of abstracting the α-proton of the ketone leading to enolization, the amine preferentially reacts with the organoboron reagent forming a strong complex, resulting in a low yield. On the other hand, in the case of strongly sterically hindered amines, such as i-Pr_3N, the large steric requirements of the amine must play a major role in the observed poor yield. Only the moderately hindered tertiary amines are efficient for quantitative enolboration.

Interesting results have also been obtained in examining the effect of the steric requirements of the amine on the enolate geometry. In general, the smaller amines favor the formation of *E* enolate, while the relatively bulkier amines favor the formation of *Z* enolate. In the present study, the smaller amines, such as Me_2EtN, Et_2MeN, and Et_3N, provide essentially the same mixture of *Z* and *E* enol borinates. Evans has also reported similar results with this reagent.[13] However, the relatively bulkier amines, such as *i*-Pr_2EtN and *i*-Pr_3N, favor the formation of *Z* enolate as compared to the smaller amines.

From this systematic study, triethylamine, favoring the formation of *E* enol borinate, and *N,N*-diisopropylethylamine, favoring the formation of *Z* enol borinate, have been selected as the most suitable amines for enolboration in terms of yield and selectivity. It is appropriate to mention here that only these two amines have been extensively employed for enolboration with the various R_2BOTf reagents.[2-4,11,12]

Comparison of Et_3N and *i*-Pr_2EtN. Most of the R_2BOTf reagents reported in the literature provide the *Z* enol borinates from ketones in the presence of either Et_3N or *i*-Pr_2EtN. The difference in the steric requirements of these two amines does not affect the enolate geometry since the smaller alkyl groups (R) and the better leaving group (OTf) on boron control the enolate geometry favoring the formation of the *Z* enol borinate. However, these amines behave quite differently in the enolboration of ketones with dialkylboron chlorides.[5a] Therefore, these two amines were compared for enolboration with the various Chx_2BX reagents (X = Cl, Br, I, OMs and OTf), using the two model ketones, diethyl ketone and propiophenone, in the hope of achieving an understanding of the effect of the steric requirements of the amine with different ketones and reagents (eq 3). The results are summarized in Table II.



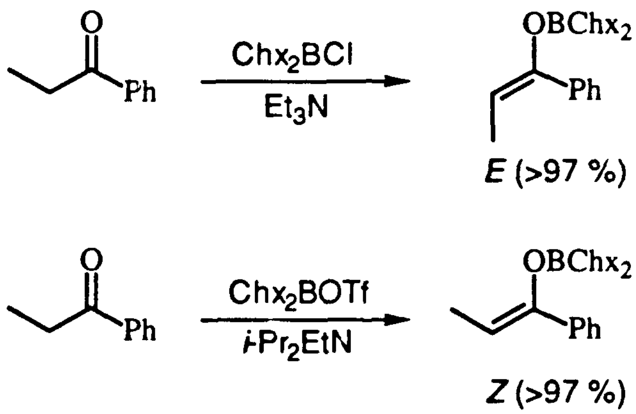
(3)

R' = Et, Ph

Chx = cyclohexyl ; X = Cl, Br, I, OMs, OTf

The results in Table II also corroborate our earlier conclusion that Et_3N, a smaller amine, favors the formation of *E* enol borinates, while *i*-Pr_2EtN, a more bulky amine, favors the formation of *Z* enol borinates, irrespective of the ketone as well as the organoboron reagent used. For example, in the enolboration of propiophenone, Chx_2BCl gives essentially exclusive *E* enolate with Et_3N, while a mixture of *Z* and *E* enolates is obtained with *i*-Pr_2EtN. On the other hand, Chx_2BOTf/Et_3N yields a mixture of *Z* and *E* enolates, whereas Chx_2BOTf/*i*-Pr_2EtN provides the isomeric *Z* enolate essentially exclusively. By a careful selection of the reagent and the amine, one can form either *Z* or *E* enol borinate selectively from propiophenone (Scheme II).

Scheme II



The results obtained in the enolboration of propiophenone with Chx_2BI are unusual, providing exclusive *Z* enol borinate, as already reported,[7b] and are independent of the amine employed for the enolization.

Effect of Solvent and Concentration. From the results in Table II, it is clear that either *Z* or *E* enol borinate can be selectively obtained from propiophenone by a careful selection of the suitable organoboron reagent and amine (Scheme II). However, in the case of diethyl ketone, only *Z* enolate has been exclusively obtained using Chx_2BX/*i*-Pr_2EtN (X = OMs or OTf) and the selective synthesis of *E* enolate could not be achieved. Only Chx_2BCl/Et_3N gives the maximimum selectivity of 79% *E* enolate among the various Chx_2BX/R''_3N reagents examined.

To improve the *E* enolate selectivity with Chx_2BCl, the best reagent, and also to attain an understanding of the effects of other reaction parameters controlling the enolate geometry, such as solvent, concentration and the reaction temperature, a systematic study was carried out for the enolboration of diethyl ketone with Chx_2BCl/Et_3N to achieve formation of *E* enol borinate (Table I). The concentration of the reaction medium was kept at 0.30 M (with respect to Chx_2BCl) for this study and the results are summarized in Table III.

The results in Table III suggest that the formation of *E* enol borinates are prefered in non-polar solvents, while the isomeric *Z* enol borinates are prefered in polar solvents. For example, 18% *Z* and 82% *E* enol borinates are realized in pentane, whereas 53% *Z* and 47% *E* enol borinates are obtained in the more polar 1,2-dichloroethane. A test reaction was also carried out using a 1:1 mixture of pentane and $(CH_2Cl)_2$, which gave 38% of *Z* and 62% of *E* enolates, in very good agreement with an average of the results obtained with the individual solvents. However, an opposite effect of the solvent polarity on the *Z/E* ratio has been reported recently in the enolization of 4-heptanone in THF-hexane mixtures using LDA.[14] Evans, from his study on the enolboration of α-chiral ethyl ketones with Chx_2BCl, has concluded that the aldol stereoselection is good in ether, poor in THF and toluene, with no enolization in CH_2Cl_2.[13] However, the present systematic study with ten different solvents of variable polarity has established a clearer picture of the effect of solvent on the yield and the stereochemistry of the enolboration. Chx_2BCl achieves a quantitative enolboration in all the solvents examined.

Little attention has been paid to the influence of the concentration in the medium used for enolboration. Our preliminary study suggests considerable control of enolate geometry with concentration. Therefore, a systematic study was carried out to achieve an understanding of the effect of concentration on the enolate geometry in the enolboration of diethyl ketone with Chx_2BCl/Et_3N. Hexane was used as the solvent in this study and the results are included in Table III.

The results indicate that the formation of *E* enol borinate is favored in dilute medium, while the formation of the isomeric *Z* enol borinate is favored in more concentrated medium. For example, about 85% *E* enol borinate has been achieved at a concentration of 0.05 M, while 78% *E* enol borinate is obtained with a higher concentration of 0.40 M. A concentration of 0.05 M is preferred to get *E* enol borinate favorably since a more dilute medium is not convenient. The highest concentration to get *Z* enol borinate is limited to 0.40 M, since stirring of the reaction mixture becomes difficult at higher concentrations due to the precipitated $Et_3N{\cdot}HCl$. This results in lower yields.

Enolboration using Chx_2BCl in the presence of a tertiary amine (R''_3N) provides the corresponding trialkylammonium chloride ($R''_3N{\cdot}HCl$) as a byproduct. This is obtained as a white precipitate in most of the solvents examined. However, it is soluble in highly polar solvents, such as $CHCl_3$, toluene, and benzene. To test if the effect of solvent on the stereochemistry is due only to its polarity difference or whether it is also influenced by the dissolved or undissolved amine salt, a test reaction was carried out as follows. The $Et_3N{\cdot}HCl$, formed in the initial enolboration of diethyl ketone with Chx_2BCl/Et_3N in hexane (0.05 M), was filtered off after centrifugation and further aldolization was carried out with the supernatant enol borinate solution. In a separate identical reaction, the aldolization was carried out without removing the amine salt. The results showed that 14% syn and 86% anti aldols were obtained in the absence of $Et_3N{\cdot}HCl$ and 15% syn and 85% anti aldols were formed in the presence of $Et_3N{\cdot}HCl$, suggesting that the byproduct amine salt has no effect on the stereochemistry and the observed solvent effect is only due to its polarity difference. All other reactions in our study, therefore, were carried out without removing the precipitated amine salt.

Effects of Temperature and Other Reaction Parameters. Most of the reported procedures suggest enolization at 0 °C. However, the aldolization procedures vary with different reagents and research groups.[3-7,13] To achieve a good kinetic aldol stereoselection, very low temperatures, such as –78 °C, have been recommended. However, good aldol stereoselection has been achieved in the case of esters using Chx_2BI/Et_3N even at 0 °C.[15] In the present study, therefore, it was decided to examine carefully the effects of both the enolization and the aldolization temperatures on the stereochemistry. The results obtained from the enolization of diethyl ketone with Chx_2BCl/Et_3N at different temperatures suggest that there is not much difference in the *Z*/*E* ratio with the enolization temperature (Table III). Essentially the same results are also obtained with the aldolization either at 0 °C or at –78 °C, if the reaction mixture is allowed to warm to room temperature. However, a considerable improvement in anti aldol selectivity was observed when the aldolization was carried out at –78 °C for 2 h, without allowing the reaction mixture to warm to room temperature. This suggests that there may be a slow isomerization of the boron aldolate over a longer period of time at higher temperature.

Different procedures for enolboration also call for different sequences for addition of the substrates. To understand if the order of addition of the various substrates affects stereochemistry, this factor was also examined. The enolization of diethyl ketone using Chx_2BCl and Et_3N in hexane (0.05 M) at 0 °C was selected for this study (eq 4).

$$\begin{aligned}
&Chx_2BCl + Et_3N \xrightarrow{\text{Ketone}} 15\,\%\,[Z] + 85\,\%\,[E] \\
&Chx_2BCl + \text{Ketone} \xrightarrow{Et_3N} 14\,\%\,[Z] + 86\,\%\,[E] \\
&\text{Ketone} + Et_3N \xrightarrow{Chx_2BCl} 17\,\%\,[Z] + 83\,\%\,[E] \qquad (4)
\end{aligned}$$

These results clearly suggest that the order of addition of substrates has only a negligible effect on the enolate geometry. Therefore, the addition of ketone to the mixture of organoboron reagent and amine has been selected as the standard procedure for our study.

It was also not very clear if the rate of addition [slow (dropwise) or fast] affects the selectivity or not. Therefore, a study on the rate of addition of ketone and aldehyde in the enolization and the aldolization steps respectively was carried out. The enolization of diethyl ketone using Chx_2BCl/Et_3N in hexane (0.05 M) at 0 °C, followed by aldolization with PhCHO at –78 °C to 25 °C, was employed for this study and the results are given below.

Rate of Addition		Stereochemistry	
Ketone	Aldehyde	*Z*/syn (%)	*E*/anti (%)
slow	slow	15	85
fast	slow	16	84
slow	fast	17	83
fast	fast	17	83

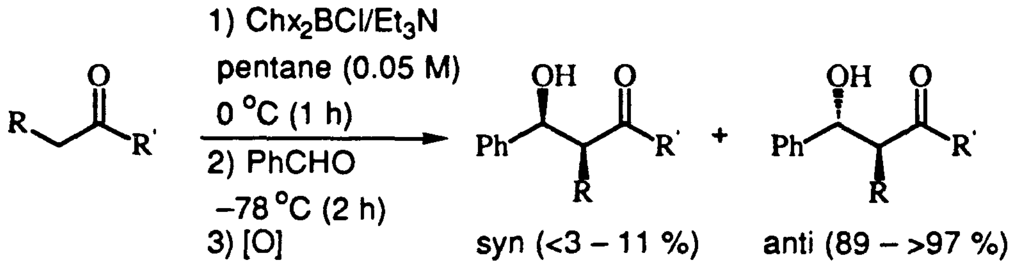
These results also clearly indicate that the stereochemistry is not affected significantly by the rate of addition of ketone and aldehyde. In the present study, however, a dropwise addition of various substrates was adopted.

Optimized Reaction Conditions to Achieve the *E* Enolate Selectivity. All these systematic studies with Chx_2BCl clearly demonstrate that the *E* enol borinates are highly favored by the use of moderately sterically hindered amines in non-polar solvents, in relatively dilute solution, while the *Z* enol borinates are favored by the relatively more hindered amines in polar solvents, in highly concentrated solution. While the enolization and the aldolization temperatures, order and rate of addition of substrates have no significant effects on the enolate/aldolate stereochemistry, aldolization at – 78 °C for 2 h without allowing the reaction mixture to warm to room temperature improves the anti aldol selectivity significantly.

The enolization of diethyl ketone with Chx_2BCl/Et_3N and subsequent aldolization with PhCHO under the optimized conditions give 95% anti aldol, a good improvement from the earlier result of 79%.[6,7] Under similar improved experimental conditions, Chx_2BCl/Me_2EtN gives 94% anti aldol and Chx_2BCl/Et_2MeN provides 93% anti aldol, essentially the same result, from diethyl ketone and benzaldehyde. With Chx_2BCl/Et_2*i*-PrN also, 86% anti aldol, an improvement from the earlier 73%, has been obtained under the new experimental conditions. This clearly suggests that the improved experimental conditions using Chx_2BCl/Et_3N to achieve the selective formation of *E* enol borinates work very well with other amines examined also.

We have previously reported the enolboration of various ketones using Chx_2BCl/Et_3N.[7a] In some cases, the formation of *E* enol borinates was achieved essentially exclusively. In other cases, however, the *E* enol borinates could not be achieved selectively. To test if the improved reaction conditions could help in achieving the selective formation of *E* enolates from other ketones, reactions were also carried out with those ketones using Chx_2BCl/Et_3N (Scheme III). The results are presented in Table IV.

Scheme III



R = Me, Et, *n*-Pr ; R' = Et, *i*-Bu, Ph, *i*-Pr, Chx, *t*-Bu, *n*-Pr, *n*-Bu

Table IV summarizes the results obtained in the enolboration of representative ketones using Chx_2BCl/Et_3N under the old and the new improved experimental conditions. These results clearly suggest that the new optimized conditions help to improve the *E* enolate selectivity from all the ketones examined and are also comparable with the results obtained with Bco_2BCl/Et_3N.[7a]

Enolboration. For the characterization and the estimation of enol borinates by ^{1}H NMR, the enolboration experiments were carried out in CCl_4 since it serves as the best solvent to analyze the products directly. This is a well established technique for the quantification of the enol borinates.[5a,6,7] In representative cases, the yields were also determined by isolating and weighing the byproduct, $R''_3N{\cdot}HX$ (X = Cl, Br, or I). In these cases, the yields were quantitative and comparable with those determined directly by ^{1}H NMR.

The olefinic protons of both *Z* and *E* enol borinates exhibit essentially identical chemical shifts and, therefore, it is very difficult to determine the *Z*/*E* ratio directly by ^{1}H NMR. The reactions of enol borinates with benzaldehyde are highly stereoselective (Scheme I), providing an indirect method to determine this ratio from the syn/anti ratio of the corresponding aldol products obtained from the reaction of enol borinates with benzaldehyde. This is also an established technique which we have been using to determine the *Z/E* ratio of the enol borinates when direct determination by ^{1}H NMR is very difficult.[5a,6,7]

Conclusions

This is a systematic study to achieve an understanding of the various effects, such as the steric requirements of the amine, the polarity of the solvent, the concentration of the medium, the temperatures of the enolization and the aldolization processes, the order and the rate of addition of the various substrates, and the presence or the absence of the byproduct amine salt, in influencing the stereochemistry of the enolboration process. A detailed investigation on the interaction of representative tertiary amines of variable steric requirements with Chx_2BCl using ^{11}B NMR suggests that the smaller amines coordinate strongly with Chx_2BCl, while the more bulky amines do not. While the smaller amines favor formation of *E* enolate, the more hindered amines favor formation of *Z* enolate. The results obtained from the enolboration of the two model ketones, diethyl ketone and propiophenone, using various Chx_2BX reagents (X = Cl, Br, I, OMs and OTf) in the presence of Et_3N and *i*-Pr_2EtN also corroborate the same conclusion. Further detailed studies infer that the *E* enol borinates are highly favored in non-polar solvents and in dilute medium, while the *Z* enol borinates are more favored in polar solvents and in relatively concentrated medium. Other effects, such as the enolization and the aldolization temperatures, the order and the rate of addition of substrates and the presence or the absence of the precipitated byproduct amine salt, have only a negligible effect on the stereochemistry. However, aldolization at –78 °C for 2 h without allowing the reaction mixture to warm to room temperature improves the anti aldol selectivity significantly. The enolboration of diethyl ketone with Chx_2BCl/Et_3N under the optimized conditions provide 95% anti aldol. This improved procedure also works very well for various ketones and tertiary amines. The enolboration of a variety of ketones with Chx_2BCl/Et_3N has also improved the anti selectivity significantly achieving 89 – >97% under the new optimized procedure. This study also helps to select the most favorable reaction conditions to obtain either *Z* or *E* enol borinates selectively.

Experimental Section

Materials. All glassware was thoroughly dried in an air oven, cooled and assembled under nitrogen for the experiments. Degassed, anhyd solvents, CH_2Cl_2, $CHCl_3$, CCl_4, $(CH_2Cl)_2$, toluene, benzene, ether, pentane and hexane were used. THF was freshly distilled from sodium benzophenone ketyl. All the commercially purchased amines were distilled over CaH_2 and used. All the ketones and amines, except for EtCO*t*-Bu, Et_2*i*-PrN and *i*-Pr_3N, were the commercial products of the highest purity available. Both ethyl *tert*-butyl ketone[6b,7a] and triisopropylamine[16a] were prepared using literature procedures. A simple method for the preparation of Et_2*i*-PrN, is described below. Detailed procedures for the synthesis of various Chx_2BX and B-X-9-BBN reagents (where X = Cl, Br, I, OMs and OTf) are described in our earlier paper.[7b] The special experimental techniques used in handling air- and moisture-sensitive compounds have been described elsewhere.[17] All of the following enolization/aldolization experiments were conducted in a 100 or 250 mL round-bottom flask capped with a rubber septum, a magnetic stirring bar, and a connecting tube attached to a mercury bubbler under a nitrogen atmosphere.

Spectra. The ^1H NMR spectra were recorded on 200 and 300-MHz instruments and the ^{11}B NMR spectra were recorded on 300-MHz instrument. The chemical shift values are in δ (ppm) relative to TMS and $BF_3{\cdot}OEt_2$ respectively.

Synthesis of Et_2*i*-PrN. To a mixture of 40.0 mL of *i*-$PrNH_2$ (465 mmol) and 35.4 g of K_2CO_3 (256 mmol) in a 250 mL round-bottom flask attached with a reflux condenser and kept at 0 °C, 78.0 mL of EtBr (1024 mmol) was added very slowly with stirring. The reaction mixture was stirred at 0 °C for 1 h and at 25 °C for 3 h. Then, it was extracted with ether, washed with water and dried over anhyd Na_2SO_4. The solvent was removed by distillation. The fractional distillation of the concentrated mixture provided >99% GC pure Et_2*i*-PrN, bp 108 °C (lit 107.5 °C)[16b] and yield 80%. The ^1H and ^{13}C NMR analyses confirmed the structure.

^{11}B NMR Study of the Interaction of Representative Amines with Chx_2BCl. A general procedure for the ^{11}B NMR study is described as follows. To a dry NMR tube kept under a N_2 atmosphere and capped with a rubber septum, 0.60 mL of Chx_2BCl solution (0.50 M in hexane, 3.00 mmol) was added using a 1 mL syringe and kept at 0 °C. To this, 0.15 mL of the amine solution (2.00 M in hexane, 3.00 mmol) was added dropwise at 0 °C using a 1 mL syringe, shaken well, kept at 0 °C for 5 min and then the ^{11}B NMR was recorded immediately.

General Procedure for the Enolization of Diethyl Ketone Using Chx_2BCl and R''_3N. To a stirred solution of Chx_2BCl (5.15 mmol), and R''_3N (5.15 mmol) in CCl_4 (17.0 mL, 0.30 M) kept at 0 °C under a N_2 atmosphere, diethyl ketone (5.00 mmol) was added dropwise. The enol borinate was generated rapidly with concurrent formation and precipitation of $R''_3N{\cdot}HCl$. An internal standard, benzene (0.50 mL, 1.00 M in CCl_4, 0.50 mmol), was added for quantification of the enol borinate by ^1H NMR analysis. The reaction mixture was stirred at 0 °C for 30 min (except for i-Pr_3N which requires a longer time) and then transferred into a centrifuge vial using a double-ended needle (18 gauge). Centrifugation resulted in the separation of the enol borinate solution from the precipitated $R''_3N{\cdot}HCl$. In representative cases, the solid $R''_3N{\cdot}HCl$ has been collected, washed, dried, and weighed. These yields were comparable with that determined directly by ^1H NMR. The enol borinate solution was then transferred into an NMR tube using a double-ended needle. The ^1H NMR analysis gave the extent of enolboration and the ^{11}B NMR (borinate region, usually broad, around 50–56 ppm) also confirmed the formation of enol borinates.

General Procedure for the Enolization of Ketones Using Chx_2BX Reagents (X = Cl, Br or I) and Et_3N or i-Pr_2EtN. To a stirred solution of Chx_2BX (5.15 mmol), and amine (Et_3N or i-Pr_2EtN, 5.15 mmol) in CCl_4 (17.0 mL, 0.30 M), kept at 0 °C under a N_2 atmosphere, the ketone (5.00 mmol) was added dropwise. The enol borinate was generated rapidly with concurrent formation and precipitation of the amine salt ($Et_3N{\cdot}HX$ or i-$Pr_2EtN{\cdot}HX$). An internal standard, benzene (0.50 mL, 1.00 M in CCl_4, 0.50 mmol), was added for quantification of the enol borinate by ^1H NMR analysis, except for propiophenone, where the aromatic ring was used as the internal standard. The reaction mixture was stirred at 0 °C for 2 h and then transferred into a centrifuge vial using a double-ended needle (18 gauge). Centrifugation resulted in the separation of the enol borinate solution from the precipitate. In representative cases, the solid amine salt has been collected, washed, dried, and weighed. Essentially quantitative yields were obtained. The enol borinate solution was then transferred into an NMR tube using a double-ended needle. The ^{1}H NMR analysis gave the extent of enolboration and the ^{11}B NMR (borinate region, usually broad, around 50–56 ppm) also confirmed the formation of enol borinates. The ^{1}H and ^{11}B NMR data of the enol borinates are given in our earlier papers.[6]

General Procedure for the Enolization of Ketones Using Chx_2BX Reagents (X = OMs or OTf) with Et_3N or *i*-Pr_2EtN. To a stirred solution of Chx_2BX (5.15 mL, 1.00 M in CCl_4, 5.15 mmol), and the amine (Et_3N or *i*-Pr_2EtN, 5.15 mmol) in CCl_4 (17.0 mL) [$CDCl_3$ is preferable for Chx_2BOMs], kept at 0 °C under a N_2 atmosphere, the ketone (5.00 mmol) was added dropwise. An internal standard, benzene (0.50 mL, 1.00 M in CCl_4, 0.50 mmol), was added for quantification of the enol borinate by ^{1}H NMR analysis, except for propiophenone, where the aromatic ring was used as the internal standard. The reaction mixture was stirred at 0 °C for 2 h and then the enol borinate solution was transferred into an NMR tube using a double-ended needle. The ^{1}H NMR analysis gave the extent of enolboration and the ^{11}B NMR (borinate region, usually broad, around 50–56 ppm) also confirmed the formation of enol borinates.

General Procedure for the Enolization of Diethyl Ketone with Chx_2BCl and Et_3N in Various Solvents and Subsequent Aldolization with PhCHO at 0 °C. To a stirred solution of Chx_2BCl (5.15 mmol), and Et_3N (5.15 mmol) in the required solvent [refer to Table III] (13 – 103 mL, 0.40 – 0.05 M) kept at 0 °C under a N_2 atmosphere, diethyl ketone (5.00 mmol) was added dropwise. The enol borinate was generated rapidly with concurrent formation and precipitation of $Et_3N{\cdot}HCl$. The reaction mixture was stirred at 0 °C for 2 h and then benzaldehyde (5.00 mmol) was added dropwise at 0 °C. The reaction mixture was stirred at 0 °C for 2 h. The absence of residual benzaldehyde confirmed the essentially quantitative formation of enol borinate, as indicated by ^{1}H NMR analysis. Then 10 mL of methanol was added at 0 °C and subsequently 1.70 mL of H_2O_2 (30%) was also added dropwise at 0 °C. The resulting mixture was stirred at 0 °C for 30 min and then at 25 °C for 3–4 h. The solvent and methanol were removed by a water aspirator (15–20 mm) and then the reaction mixture was extracted with ether, washed with water, and then dried over anhyd Na_2SO_4. The ether was removed and the products were analyzed as such by ^1H NMR (in $CDCl_3$) to determine the syn/anti ratio.

General Procedure for the Enolization of Diethyl Ketone with Chx_2BCl and Et_3N in Various Solvents and Subsequent Aldolization with PhCHO at –78 °C. To a stirred solution of Chx_2BCl (5.15 mmol), and Et_3N (5.15 mmol) in the required solvent [refer to Table III] (13 – 103 mL, 0.40 – 0.05 M) kept at the required temperature [refer to Table III] under a N_2 atmosphere, diethyl ketone (5.00 mmol) was added dropwise. The enol borinate was generated rapidly with concurrent formation and precipitation of $Et_3N{\cdot}HCl$. The reaction mixture was stirred at this temperature for 2–3 h and then benzaldehyde (5.00 mmol) was added dropwise at –78 °C. The reaction mixture was stirred at this temperature for 2–3 h and then allowed to warm slowly to room temperature overnight with constant stirring. The absence of residual PhCHO confirmed the essentially quantitative formation of enol borinate, as indicated by ^1H NMR analysis. Then 10 mL of methanol was added at 0 °C and subsequently 1.70 mL of H_2O_2 (30%) was also added dropwise at 0 °C. The resulting mixture was stirred at 0 °C for 30 min and then at 25 °C for 3–4 h. The solvent and methanol were removed by a water aspirator (15–20 mm) and then the reaction mixture was extracted with ether, washed with water, and then dried over anhyd Na_2SO_4. The ether was removed and the products were analyzed as such by ^1H NMR (in $CDCl_3$) to determine the syn/anti ratio.

General Procedure for the Enolization of Diethyl Ketone with Chx_2BCl and Et_3N and Subsequent Aldolization with PhCHO in the Absence of the Precipitated $Et_3N{\cdot}HCl$. To a stirred solution of Chx_2BCl (5.15 mmol), and Et_3N (5.15 mmol) in hexane (103 mL, 0.05 M) kept at 0 °C under a N_2 atmosphere, diethyl ketone (5.00 mmol) was added dropwise. The enol borinate was generated rapidly with concurrent formation and precipitation of $Et_3N{\cdot}HCl$. The reaction mixture was stirred at 0 °C for 2 h and then transferred into a centrifuge vial using a double-ended needle (18 gauge). Centrifugation resulted in the separation of the enol borinate solution from the precipitated $Et_3N \cdot HCl$. The supernatant enol borinate solution was transferred back into a dry round-bottom flask using a double-ended needle (18 gauge). Then, benzaldehyde (5.00 mmol) was added dropwise to this enol borinate solution at –78 °C. The reaction mixture was stirred at this temperature for 2–3 h and then allowed to warm slowly to room temperature overnight with constant stirring. Then 10 mL of methanol was added at 0 °C and subsequently 1.70 mL of H_2O_2 (30%) was also added dropwise at 0 °C. The resulting mixture was stirred at 0 °C for 30 min and then at 25 °C for 3–4 h. The solvent and methanol were removed by a water aspirator (15–20 mm) and then the reaction mixture was extracted with ether, washed with water, and then dried over anhyd Na_2SO_4. The ether was removed and the products were analyzed as such by ^1H NMR (in $CDCl_3$) to determine the syn/anti ratio.

General Procedure for the Aldolization of the Enol Borinates, Generated Using Chx_2BCl and R''_3N, with PhCHO. To a solution of enol borinate in hexane (0.30 M) generated under a N_2 atmosphere from 5.00 mmol of the ketone at 0 °C using Chx_2BCl and R''_3N as described above, benzaldehyde (5.00 mmol) was added dropwise at –78 °C. The reaction mixture was stirred at this temperature for 2–3 h and then allowed to warm slowly to room temperature overnight with constant stirring. Then 10 mL of methanol was added at 0 °C and subsequently 1.70 mL of H_2O_2 (30%) was also added dropwise at 0 °C. The resulting mixture was stirred at 0 °C for 30 min and then at 25 °C for 3–4 h. The solvent and methanol were removed by a water aspirator (15–20 mm) and then the reaction mixture was extracted with ether, washed with water, and then dried over anhyd Na_2SO_4. The ether was removed and the products were analyzed as such by ^1H NMR (in $CDCl_3$) to determine the syn/anti ratio.

General Procedure for the Aldolization of the Enol Borinates, Generated Using Chx_2BX Reagents (Except for X = I) and Et_3N or *i*-Pr_2EtN, with PhCHO. To a solution of enol borinate in hexane (0.30 M) generated under a N_2 atmosphere from 5.00 mmol of the ketone at 0 °C using Chx_2BX reagents (except for X = I) and Et_3N or *i*-Pr_2EtN as described above, benzaldehyde (5.00 mmol) was added dropwise at –78 °C. The reaction mixture was stirred at this temperature for 2–3 h and then allowed to warm slowly to room temperature overnight with constant stirring. The absence of residual benzaldehyde confirmed the essentially quantitative formation of enol borinate, as indicated by ^1H NMR analysis. Then 10 mL of methanol was added at 0 °C and subsequently 1.70 mL of H_2O_2 (30%) was also added dropwise at 0 °C. The resulting mixture was stirred at 0 °C for 30 min and then at 25 °C for 3–4 h. The solvent and methanol were removed by a water aspirator (15–20 mm) and then the reaction mixture was extracted with ether, washed with water, and then dried over anhyd Na_2SO_4. The ether was removed and the products were analyzed as such by ^1H NMR (in $CDCl_3$) to determine the syn/anti ratio.

General Procedure for the Aldolization of the Enol Borinates, Generated Using Chx_2BI and Et_3N or *i*-Pr_2EtN, with PhCHO. To a solution of enol borinate in hexane (0.30 M) generated under a N_2 atmosphere from 5.00 mmol of the ketone at 0 °C using Chx_2BI and Et_3N or *i*-Pr_2EtN as described above, benzaldehyde (5.00 mmol) was added dropwise at −78 °C. The reaction mixture was stirred at this temperature for 2–3 h and then allowed to warm slowly to room temperature overnight with constant stirring. Then 10 mL of methanol was added at 0 °C and subsequently 2.50 mL of H_2O_2 (30%) was also added dropwise at 0 °C [Oxidation of the reaction mixtures containing the boron aldolates produced from Chx_2BI requires excess H_2O_2 (2.50 mL in place of the 1.70 mL used for the other Chx_2BX reagents). The excess hydrogen peroxide is necessary because the iodide, present as $Et_3N{\cdot}HI$ or *i*-$Pr_2EtN{\cdot}HI$, also gets oxidized to iodine]. The resulting mixture was stirred at 0 °C for 30 min and then at 25 °C for 3–4 h. The solvent and methanol were removed by a water aspirator (15–20 mm) and then the reaction mixture was extracted with ether. The dark-colored ether solution containing iodine was washed with dilute sodium thiosulfate solution and water. The colorless ether solution was dried over anhyd Na_2SO_4, the ether was evaporated and the products were analyzed as such by ^1H NMR (in $CDCl_3$) to determine the syn/anti ratio.

Optimized Procedure for the Stereoselective Synthesis of Anti Aldols Using Chx_2BCl/Et_3N. A general optimized procedure to achieve either exclusive or predominant anti aldols using Chx_2BCl/Et_3N is described as follows. To a stirred solution of Chx_2BCl (5.15

mmol), and Et_3N (5.15 mmol) in pentane (103 mL, 0.05 M) kept at 0 °C (except for EtCO*t*-Bu which requires 25 °C for 48 h) under a N_2 atmosphere, the ketone (5.00 mmol) was added dropwise. The enol borinate was generated rapidly with concurrent formation and precipitation of $Et_3N{\cdot}HCl$. The reaction mixture was stirred at 0 °C for 1 h. Then, benzaldehyde (5.00 mmol) was added dropwise at –78 °C and the reaction mixture was stirred at this temperature for 2 h. About 10 mL of methanol was added at –78 °C and subsequently 1.70 mL of H_2O_2 (30%) was also added dropwise at –78 °C. The resulting mixture was then stirred at 0 °C for 30 min and at 25 °C for 3–4 h. The solvent and methanol were removed by a water aspirator (15–20 mm) and the reaction mixture was extracted with ether, washed with water, and then dried over anhyd Na_2SO_4. The ether was removed and the products were analyzed as such by ^1H NMR (in $CDCl_3$) to determine the syn/anti ratio. The ^1H NMR data of both syn and anti aldols are given in our earlier paper.[7a]

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Supplementary Material Available: ^{11}B NMR spectra (7 pages) of Chx_2BCl and its interaction with the various tertiary amines and also representative ^1H NMR spectra (31 pages) of the benzaldehyde aldol products of the enol borinates representing each study (totally 38 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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Table I. ^{11}B NMR Study on the Interaction of Representative Tertiary Amines with Chx_2BCl and the Effect of the Steric Requirements of the Amine on the Enolate Geometry in the Enolboration of Diethyl Ketone with Chx_2BCl[a,b]

amine	^{11}B NMR (δ ppm)[d,e]	coordination	enolate geometry (%)[c] Z	E	yield[f,g]
Me_2EtN[h]	47.49	strong	24	76	54
Et_2MeN[i]	75.95	weak	23	77	68
Et_3N	76.32	no	21	79	75
Et_2*i*-PrN	76.35	no	27	73	65
i-Pr_2EtN	76.35	no	40	60	53
i-Pr_3N[j]	76.35	no	69	31	12

[a]Enolizations and subsequent aldolizations with PhCHO were carried out in hexane (0.30 M) at 0 °C (30 min) and at –78 °C (allowed to warm slowly to room temperature) respectively unless otherwise stated. [b]In cases where the spectrum shows only one major isomer, we have indicated the minor isomer to be <3% since such small peaks may be lost in the background. [c]Z/E ratio was determined on the basis of the syn/anti ratio of their corresponding PhCHO aldol products [benzylic proton, syn at δ 5.02 ppm (d, J = 4.4 Hz) and anti at δ 4.74 ppm (d, J = 8.4 Hz)]. [d]Chx_2BCl (hexane, 0.50 M) = δ 76.49 ppm [a small impurity peak (<1 %) appeared around δ 41 ppm]. [e]^{11}B NMR study was carried out using Chx_2BCl : amine = 1:1 in hexane (0.50 M). [f]Determined by ^{1}H NMR. [g]The yields were also confirmed by collecting and weighing the precipitated amine salt. [h]A white precipitate, due to a strong complex formation, was observed. [i]A small peak (<3 %) also appeared at δ 52.07 ppm. [j]Reaction at 0 °C for 3 h.

Table II. Comparison of Et_3N and *i*-Pr_2EtN in the Stereoselective Enolboration of Diethyl Ketone and Propiophenone with Various Chx_2BX Reagents[a,b]

		diethyl ketone (%)[c]			propiophenone (%)[d]		
Chx_2BX	amine	*Z*	*E*	yield[e,f]	*Z*	*E*	yield[e,f]
Chx_2BCl	Et_3N	21	79	97	<3	>97	97
	i-Pr_2EtN	40	60	93	51	49	94
Chx_2BBr	Et_3N	30	70	96	5	95	97
	i-Pr_2EtN	51	49	92	57	43	93
Chx_2BI	Et_3N	56	44	97	>97	<3	97
	i-Pr_2EtN	76	24	94	>97	<3	95
Chx_2BOMs	Et_3N	80	20	93	62	38	95
	i-Pr_2EtN	>97	<3	89	>97	<3	93
Chx_2BOTf	Et_3N	80	20	96	67	33	96
	i-Pr_2EtN	>97	<3	93	>97	<3	95

[a]Enolizations and subsequent aldolizations with PhCHO were carried out in hexane (0.30 M) at 0 °C (2 h) and at –78 °C (allowed to warm slowly to room temperature) respectively unless otherwise stated. [b]Refer to footnote *b* of Table I. [c]Refer to footnote *c* of Table I. [d]*Z*/*E* ratio was determined on the basis of the syn/anti ratio of their corresponding PhCHO aldol products [benzylic proton, syn at δ 5.23 ppm (d, *J* = 3.0 Hz) and anti at δ 4.98 ppm (d, *J* = 8.1 Hz)]. [e]Determined by ^1H NMR. [f]The yields were also confirmed by collecting and weighing the precipitated $R''_3N{\cdot}HX$ (where X = Cl, Br or I).

Table III. Effects of Solvent, Concentration and Reaction Temperature on the Enolate/Aldolate Stereochemistry in the Enolboration of Diethyl Ketone with Chx_2BCl/Et_3N

solvent	concentration (M)[a]	temperature (°C) enol[b]	temperature (°C) aldol[c]	stereochemistry (%) Z/syn	stereochemistry (%) E/anti	stereochemistry (%) yield[d]
$(CH_2Cl)_2$	0.30	0	0[e]	53	47	95
CH_2Cl_2	0.30	0	–78	45	55	97
$CHCl_3$	0.30	0	0[e]	44	56	93
THF	0.30	0	–78	43	57	96
toluene	0.30	0	–78	36	64	95
benzene	0.30	0	0[e]	35	65	95
ether	0.30	0	–78	26	74	96
CCl_4	0.30	0	0[e]	23	77	96
hexane	0.30	0	–78	21	79	97
	0.40	0	–78	22	78	90
	0.20	0	–78	17	83	97
	0.10	0	–78	18	82	97
	0.05	0	–78	15	85	97
	0.05	25	–78	16	84	97
	0.05	–78[f]	–78	16	84	93
	0.05	0	0[e]	17	83	97
	0.05	0	–78[g]	10	90	96
pentane	0.30	0	–78	18	82	97
	0.05	0	–78[g]	5	95	97

[a]With respect to Chx_2BCl. [b]Enolization for 2 h unless otherwise stated. [c]Stirred at –78 °C for 2–3 h and then allowed to warm slowly to room temperature overnight unless otherwise stated. [d]Determined by ^1H NMR. [e]Aldolization at 0 °C for 2 h. [f]Enolization at –78 °C for 3 h. [g]Aldolization at –78 °C for 2 h.

Table IV. Comparison of the Results Using the Old and the New Reaction Conditions in the Enolboration of Representative Ketones with Chx_2BCl/Et_3N[a,b]

RCOR'		old (%)[c]			new (%)[d]		
R	R'	*Z*	*E*	yield[e]	*Z*	*E*	yield[e]
Et	Et	21	79	97	5	95	97
Et	*i*-Bu	17	83	96	8	92	97
Et	Ph	<3	>97	97	<3	>97	97
Et	*i*-Pr	<3	>97	95	<3	>97	95
Et	Chx	<3	>97	96	<3	>97	96
Et	*t*-Bu[f]	<3	>97	60	<3	>97	75
n-Pr	*n*-Pr	20	80	95	6	94	96
n-Bu	*n*-Bu	29	71	95	11	89	95

[a]*Z*/*E* ratio was determined on the basis of the syn/anti ratio of their corresponding PhCHO aldol products. [b]Refer to footnote *b* of Table I. [c]Enolizations at 0 °C in hexane (0.30 M) for 1 h and subsequent aldolizations with PhCHO at –78 °C for 2–3 h and then allowing the reaction mixture to warm slowly to room temperature unless otherwise stated [ref. 7(a)]. [d]Enolizations at 0 °C in pentane (0.05 M) for 1 h and subsequent aldolizations with PhCHO at –78 °C for 2 h unless otherwise stated. [e]Refer to footnotes *f* and *g* of Table I. [f]Enolization at 25 °C for 48 h.